



34/ Appeal
Brief 3
PATENT

Customer No. 22,852
Attorney Docket No. 5725.0213-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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In re Application of:)
)
Paolo GIACOMONI)
)
Application No. 08/894,788) Group Art Unit: 1615
)
CPA Filed: February 9, 2000) Examiner: L. Channavajjala
)
For: NITRIC OXIDE SYNTHASE)
INHIBITORS)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Further to of the Notice of Appeal filed concurrently herewith, and pursuant to 37 C.F.R. § 1.192, Appellant presents in triplicate a brief accompanied by the fee of \$320.00 required under 37 C.F.R. § 1.17(c).

This appeal is in response to the Office Action dated April 23, 2003, containing at least the second rejection of claims 31-38, 40-54, and 56-66, which claims are set forth in the attached Appendix. If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to our Deposit Account No. 06-0916.

(1) REAL PARTIES IN INTEREST

L'Oréal is the assignee of record.

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(2) RELATED APPEALS AND INTERFERENCES

None. Appellant notes, however, that the claims presently appealed were previously appealed by the brief filed May 21, 2001, which was given Appeal No. 2002-1494. See Paper No. 30. However, due to the Examiner improperly entering a Supplemental Examiner's Answer dated September 21, 2001 (Paper No. 29), the application was remanded to the Examiner for reconsideration. *Id.* The Examiner responded by issuing the April 23, 2003, Office Action, wherein the Examiner made the same rejection of claims as was previously appealed in Appeal No. 2002-1449. Subsequent to the current rejection of claims 31-38, 40-54, and 56-66, this appeal was filed.

(3) STATUS OF CLAIMS

Claims 31-38, 40-54, and 56-66 are pending in this application. No claim has been allowed. Claims 1-30, 39, and 55 were previously canceled without prejudice to or disclaimer of the subject matter contained therein. Claims 31-38, 40-54, and 56-66 have been at least twice rejected under 35 U.S.C. § 103(a). See 37 C.F.R. § 1.191(a).

(4) STATUS OF AMENDMENTS

The Preliminary Amendment filed on August 25, 1997, and the Amendments filed on May 4, 1998, December 9, 1999, and July 13, 2000, have been entered. No

Amendment after Final was filed. No Amendment was made during the reconsideration period subsequent to the first appeal.

(5) SUMMARY OF THE INVENTION

The present invention relates to a cosmetic or pharmaceutical composition comprising an amount of a nitric oxide synthase inhibitor effective to reduce the cutaneous irritant effect of topical products containing components which irritate the skin. The invention also relates to a method for reducing the cutaneous irritant effect comprising including in a cosmetic or pharmaceutical composition an effective amount of a nitric oxide synthase inhibitor. Finally, the invention relates to a cosmetic or pharmaceutical treatment comprising applying to the skin, scalp, nails, or mucous membranes an effective amount of a cosmetic or pharmaceutical product comprising a nitric oxide synthase inhibitor and at least one component which irritates the skin, scalp, nails, or mucous membranes.

It is common for cosmetic and pharmaceutical products to contain components which have beneficial effects (e.g., sunscreens, vitamins, active agents, surfactants, preservatives, perfumes, solvents, or propellants), but which may have an irritating effect as well. Often, this irritating effect is manifested as blotches, pain, edema, inflammation, or a burning, itching, or "pricking" sensation. When the cosmetic or pharmaceutical product is applied, it can react with pre-existing substances in the cells and tissues, and/or liberate certain intracellular substances, thus causing the irritating

manifestations described above. Consequently, although it is desired to include these components in cosmetic or pharmaceutical products for their beneficial effect, there is a need to limit or suppress their irritating effect.

Appellant has surprisingly discovered that nitric oxide synthase inhibitors effectively limit, and often even suppress, the irritating effect of these beneficial components. Accordingly, by including an effective amount of a nitric oxide synthase inhibitor in a cosmetic or pharmaceutical product, Appellant has been able to minimize the irritating effect caused by including these components and allow their beneficial effect to be maximized.

(6) ISSUE

Whether claims 31-38, 40-54, and 56-66 are patentable under 35 U.S.C. § 103 over (1) U.S. Patent No. 5,716,625 to Hahn et al. ("Hahn") in view of U.S. Patent No. 5,358,969 to Williamson et al. ("Williamson"), (2) Hahn in view of U.S. Patent No. 5,449,688 to Wahl et al. ("Wahl"), or (3) Hahn in view of Williamson and Wahl.

(7) GROUPING OF CLAIMS

Each claim of this patent application is separately patentable, and upon issuance of a patent will be entitled to a separate presumption of validity under 35 U.S.C. § 282.

For convenience in handling this Appeal, the claims have been grouped together.

Thus, pursuant to 37 C.F.R. § 1.192(c)(7), in this Appeal, the rejected claims will stand

or fall together.

(8) ARGUMENTS

Claims 31-38, 40-54, and 56-66 are rejected under 35 U.S.C. § 103(a) over Hahn in view of Williamson, Hahn in view of Wahl, or Hahn in view of Williamson and Wahl. The Examiner asserts that Hahn teaches the general theory of combining an irritant with an anti-irritant in a cosmetic or pharmaceutical composition, and that Williamson and Wahl teach nitric oxide synthase inhibitors for the treatment of various acute or chronic inflammatory conditions. Thus, the Examiner concludes that a cosmetic or pharmaceutical composition combining the nitric oxide synthase inhibitors of Williamson and Wahl with an irritant would have been obvious, in light of the teachings of Hahn. See, e.g., April 23, 2003, Office Action. Appellant respectfully disagrees.

A. Factual Inquires to Determine Obviousness

Several basic factual inquiries must be made by the Examiner in order to determine the obviousness or non-obviousness of claims of a patent application under 35 U.S.C. § 103. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). In order to carry the initial burden of establishing a *prima facie* case of obviousness that satisfies the *Graham* standard, the Examiner must show that (1) all of Appellant's elements are disclosed by the prior art references, (2) there exists some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings in the manner proposed, and (3) there is a reasonable expectation of success in such a combination or modification. See M.P.E.P. § 2143. For the reasons set forth below, the Examiner has failed to meet her burden of establishing a *prima facie* case of obviousness, as not all of these required criteria have been satisfied. Therefore the rejections under 35 U.S.C. § 103(a) are improper and should be reversed.

**B. The Cited References Do Not Provide
Any Motivation For Their Combination**

Claim 31 of the present application recites:

"[a] cosmetic or pharmaceutical composition comprising, in a cosmetically or pharmaceutically acceptable medium, at least one cosmetic or pharmaceutical product capable of causing a cutaneous irritant effect and at least one nitric oxide synthase inhibitor, wherein said nitric oxide synthase inhibitor is present in an amount effective to reduce the cutaneous irritant effect of the at least one cosmetic or pharmaceutical product."

Claims 32-38, 40-47, and 65 depend either directly or indirectly from claim 31.

Method claim 48 recites:

"[a] method for reducing the cutaneous irritant effect of a topically applied cosmetic or pharmaceutical composition containing at least one cosmetic or pharmaceutical product capable of having an irritant character on the skin, the scalp, the nails, or the mucous membranes, wherein said method comprises applying said composition to the skin, scalp, nails,

or mucous membranes, wherein said cosmetic or pharmaceutical composition further comprises at least one nitric oxide synthase inhibitor in an amount effective to reduce the cutaneous irritant effect of said at least one cosmetic or pharmaceutical product."

Claims 49-54, 56-62, and 66 depend either directly or indirectly from claim 48.

Claims 63 and 64 recite a process for the cosmetic and pharmaceutical treatment, respectively,

"of the skin, scalp, nails, or mucous membranes comprising applying a cosmetic composition according to claim 31 to said skin, scalp, nails, or mucous membranes."

Hahn, the primary reference, teaches topical formulations comprising an aqueous soluble strontium (II) metal cation, which has an anti-irritant effect, wherein said formulations may optionally also contain an irritant, and methods for using the same to inhibit skin irritation upon application. See, e.g., abstract and column 10, lines 43-47. However, as the Examiner has recognized, Hahn does not disclose the use of a nitric oxide synthase inhibitor as an anti-irritant, as in the presently claimed invention. See, e.g., April 23, 2003, Office Action, at page 2.

Indeed, Hahn is not generic with respect to teaching anti-irritants, and nowhere does it suggest the substitution of the strontium (II) metal cation with any other anti-irritant. The Examiner has not pointed to any teaching or suggestion in Hahn that would have motivated the skilled artisan to replace the strontium (II) metal cation of Hahn with another anti-irritant—and certainly not with a nitric oxide synthase inhibitor. Recognizing this deficiency of Hahn, the Examiner relies on either Williamson or Wahl, or the

combination of the two, to supply the requisite motivation for substituting the strontium (II) metal cation with a nitric oxide synthase inhibitor. According to the Examiner, the fact that Hahn and Williamson allegedly "teach the treatment of [the] same skin conditions" renders obvious the substitution of the strontium (II) cation of Hahn with the nitric oxide synthase inhibitor of Williamson or Wahl. See April 23, 2003, Office Action at page 5. This argument has at least two major flaws, however, and therefore cannot support a finding of *prima facie* obviousness.

First, the Examiner's argument improperly fails to consider the teachings of the references "as a whole," as both the M.P.E.P. and case law mandate. A reference must be considered for everything it teaches, and not just that which will support a given argument to the exclusion of other parts necessary to the full appreciation of what the reference fairly suggests to one of ordinary skill in the art. M.P.E.P. § 2141; *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448-49, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986) (holding that, by failing to consider a prior art reference in its entirety, the district court ignored portions of the reference that led away from obviousness); *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997). In the present case, Hahn discloses one method of treatment using one compound for one condition, while both Williamson and Wahl disclose a different method of treatment using a different compound for a different condition, and thus, as a whole, do not motivate their combination or modification.

As discussed above, Hahn teaches localized administration of topical compositions containing strontium (II) metal cation, where the strontium (II) cation counteracts superficial skin irritation caused by topical application of a cosmetic or pharmaceutical product. See, e.g., abstract and column 10, lines 43-47. In contrast, both Williamson and Wahl are directed to systemic administration of specific amino acids and derivatives thereof, for treating or preventing acute or chronic inflammatory diseases caused by intracellular nitric oxide production. See Williamson, column 3, lines 13-22; Wahl, column 1, lines 15-63.

Specifically, Wahl discusses, in detail, the importance of limiting or inhibiting nitric oxide production by leukocytes, i.e., white blood cells. The reference explains that when a leukocyte is activated by bacteria, fungi, or tumor cells, it responds by converting arginine, an amino acid, into a nitric oxide free radical via the action of a nitric oxide synthase. See Wahl, column 1, lines 15-36. This nitric oxide free radical then aids the leukocyte in killing the invading bacteria, fungi, or tumor cells. *Id.*

However, as taught by both Wahl and Williamson, excessive nitric oxide can also damage healthy cells in the area of the nitric oxide release, and can actually suppress the host's defenses, leading to various inflammatory conditions or diseases, such as, for example, rheumatoid arthritis or uveitis. See Wahl, column 1, lines 44-36; Williamson, column 3, lines 13-22. Thus, it is desirable to decrease the amount of nitric oxide released by the cells, as a means of preventing and treating chronic and acute inflammatory conditions which are caused by excess nitric oxide attacking the healthy

cells. See, e.g., Wahl, columns 1, line 64 to column 2, line 2; Williamson, column 3, lines 13-44.

Accordingly, both Williamson and Wahl disclose systemic methods of treating or preventing inflammatory diseases caused by excess nitric oxide, by decreasing or preventing nitric oxide formation within the cells by way of nitric oxide synthase inhibitors. Hahn, however, is not directed to systemically decreasing or preventing nitric oxide formation in the cells at all, let alone by the use of nitric oxide synthase inhibitors; rather, Hahn is directed to the use of a metal cation for counteracting superficial skin irritation caused by topically applied skin irritants. In other words, when viewed **as a whole**, the references do not motivate their combination, as Williamson and Wahl are directed to treating one problem with one solution, while Hahn is directed to treating a distinctly different problem with a distinctly different solution—a fact which the Examiner appears to have disregarded.

Instead, the Examiner has maintained that the motivation to combine Hahn with Williamson, Wahl, or both, comes from the general theory of combining a skin irritant with an anti-irritant, as taught by Hahn, and the alleged teaching by Williamson and Wahl that nitric oxide synthase inhibitors are useful in treating “skin conditions” resulting from irritation. See, e.g., April 23, 2003, Office Action, at pages 2-3. Appellant submits that this statement clearly demonstrates that the Examiner is picking and choosing individual parts of the references to support her position, while ignoring the overall teaching of the references as a whole, i.e., that (1) Hahn teaches localized

administration of a metal cation for counteracting topically induced skin irritation or inflammation, whereas (2) Williamson and Wahl teach systemic administration of nitric oxide synthase inhibitors for preventing inflammation resulting from intracellular formation of nitric oxide.

Thus, even assuming, *arguendo*, that the Examiner is correct and that Williamson and Wahl do teach that the nitric oxide synthase inhibitors disclosed therein are useful for treating skin conditions, the references as a whole are directed to a solution to the problem of skin conditions caused by the formation of nitric oxide within the cells, and not by any topically applied irritant, as in Hahn.

Second, the Examiner's argument is apparently premised upon the contention that "a skilled artisan would have been motivated to incorporate any anti-irritant in place of the strontium cation in the teachings of Hahn." See, e.g., April 19, 2000, Office Action at page 4; see also April 23, 2003, Office Action at pages 4-5 (maintaining that it would be "obvious" to replace the particular strontium (II) cation of Hahn with the particular nitric oxide synthase inhibitor of Williamson or Wahl because "Hahn states that it is highly desirable to identify compounds with anti-irritant activity"). That one of ordinary skill in the art would have been motivated to try innumerable anti-irritants in the compositions of Hahn, as suggested by the Examiner, finds no support in the law. As the Examiner is aware, whether a modification would have been "obvious to try" is a legally improper standard for determining obviousness. See *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). When there are, as in this situation,

innumerable possible anti-irritants, there must be some motivation toward a specific anti-irritant in order to support a *prima facie* case of obviousness. No such motivation has been demonstrated in the present case.

Accordingly, as (1) Hahn and Williamson/Wahl are directed to solving distinctly different problems by distinctly different mechanisms, and (2) at most, the skilled artisan would have been motivated to try combining or modifying the references in the manner which the Examiner asserts would have been obvious, along with innumerable other combinations or modifications, the rejection is legally improper and should be reversed.

C. The Examiner has not Demonstrated That any Reasonable Expectation of Success in the Proposed Combination Exists

Further, no reasonable expectation of success in the Examiner's proposed combination or modification exists. Indeed, the Examiner has not even pointed to any basis for such an expectation by one of ordinary skill in the art. As discussed above, under the Examiner's logic, any anti-irritant could be substituted for the strontium (II) cation of Hahn. In fact, since the irritant of Hahn is not specified, the Examiner presumes that any anti-irritant will counteract any irritation in any cosmetic or dermatological composition.

However, one of ordinary skill in the art would have no basis for knowing, without the benefit of the present disclosure, that the presently claimed nitric oxide synthase inhibitors, which affect the formation of nitric oxide in the cell, would be effective for treating skin irritation caused by topically applied products.

One of ordinary skill in the art would not have had any reason to expect that the strontium (II) cation and the nitric oxide synthase inhibitor were interchangeable, nor has the Examiner pointed to any such reason, as she must to satisfy her burden. Appellant points out that the anti-irritant of Hahn is a metal cation, whereas the nitric oxide synthase inhibitors of Williamson and Wahl are amino acids or derivatives thereof. The chemistry involved in the activity of these anti-irritants is simply different. None of the references cited teach or suggest that a metal cation and an amino acid would be interchangeable in any composition, let alone in the composition of Hahn, nor has the Examiner pointed to any such suggestion. In fact, one of ordinary skill in the art would most likely believe that these very different components would **not** be interchangeable for any purpose in any composition, as strontium is an elemental metal, while amino acids, primarily comprising nitrogen, carbon, oxygen, and hydrogen, are the building blocks of proteins.

Notably, Hahn teaches the unpredictability in the expectation that any other anti-irritant agent would be interchangeable with the strontium (II) metal cation disclosed therein: "A number of factors make it difficult to predict what effects, if any, particular agents. . . may have on nerve activity and sensation in intact animal bodies." See column 6, line 55 to column 8, line 67. In light of this teaching, the skilled artisan would have had no reason to expect that the anti-irritants of Wahl and Williamson would have been successful in the composition of Hahn.

Further, rather than supporting such a substitution of anti-irritants, Hahn actually teaches that there is **no** reasonable expectation of success, as the reference **teaches away from** the substitution that the Examiner has concluded is obvious: "[a]gents which are effective to combat one source of sensory stimulus-for example steroidal agents to treat skin inflammation-are ineffective against other sensory stimuli such as pressure, heat, or the transitory sting or itch caused by an applied skin care product." *Id.*

Accordingly, as there is no reasonable expectation of success in the combination or modification of these references, and in fact, the references themselves actually teach that the modification or combination the Examiner suggests would not have been successful, the rejection is legally improper and should therefore be reversed.

D. The Examiner Has Used Improper Hindsight in Her Evaluation

The Federal Circuit has held that using Appellant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of § 103 of judging obviousness at the point in time when the invention was made. *See Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988). As discussed in detail above, Hahn and Williamson/Wahl are directed to distinctly different solutions to distinctly different problems using distinctly different mechanisms. None of the references teach or suggest that the claimed nitric oxide synthase inhibitors would be useful for counteracting the irritation caused by topically applied irritants, and thus, the

motivation to combine the references and the expectation of success could have only come from Appellant's disclosure. Accordingly, as the Examiner has failed to point to any teaching or suggestion in any of the references or in the knowledge of those skilled in the cosmetic art that supports any motivation to modify or combine the references in the manner proposed, it is Appellant's position that the Examiner has impermissibly used hindsight reconstruction, after viewing Appellant's disclosure, in making her determination that the combination of Hahn and Williamson, Wahl, or both, would have been obvious. Accordingly, the rejection is legally improper and should be reversed.

In light of the foregoing remarks, Appellant submits that the rejections under 35 U.S.C. § 103 over (1) Hahn in view of Williamson, (2) Hahn in view of Wahl, or (3) Hahn in view of Williamson and Wahl are improper, and respectfully requests that these rejections be reversed.

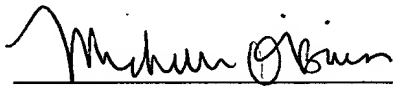
(9) CONCLUSION

For the reasons set forth above, Appellant maintains that a *prima facie* case of obviousness has not been established by the Examiner over the cited references, taken alone or in combination. The Examiner has failed to demonstrate the motivation necessary to combine the references in the manner suggested by the Examiner, or that any reasonable expectation of success in their combination exists. Additionally, the Examiner has improperly used hindsight in her evaluation of obviousness, and thus, her conclusion and rejections are improper.

Accordingly, Appellant respectfully requests reversal of the rejection of claims
31-38, 40-54, and 56-66 under 35 U.S.C. § 103.

Respectfully submitted,

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